REMARKS

Applicants would like to thank the Examiner for the courteous and productive interview on May 7, 1996. The content of the interview is discussed in detail below.

Affirmation of the election

During a telephone conversation with Carolyn Elmore on October 3, 1994, a provisional election of species was made with traverse to prosecute the invention directed to herpesvirus mutations in the ICP8 gene. Applicants' Agent affirms this election. It is noted with appreciation that the restriction between Claim 31 and Claims 1-30 and 32 has been withdrawn.

With regard to the election of species, Applicants request clarification of the requirement. The Office action implies that the claims are directed to ICP8 and ICP27. The claims are actually drawn to compositions and uses of herpesviruses which are mutated in genes encoding proteins, e.g. ICP8 and ICP27, such that the proteins are not expressed in a functional manner, if at all. These proteins are not relied upon in the invention to elicit an immunomodulatory or protective immune response upon administration. As such, the antigenicity of the proteins are not relevant to the invention.

Furthermore, since the listed species share the same classification, there is no significant burden in searching the species together. Thus, withdrawal of the election of species between proteins essential for viral replication is requested.

Clarification of Claim 4

The Examiner states that Claim 4 is directed to a mutation in the gene encoding the ICP28 protein which appears to be a typographical error. The Examiner requests clarification.

Our records indicate that Claim 4 relates to a pharmaceutical composition wherein the mutation is in the gene or genes encoding the proteins ICP8 or ICP27 as described in the specification (see page 3, line 16). Thus, the amendment to Claim 4 suggested by the Examiner is not necessary.

Provisional Rejection of Claims 1-26 and 29-32 under 35 U.S.C. § 101

Claims 1-26 and 29-32 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of Claims 1-26 and 29-32 of co-pending application Serial No. 08/179,106. It is noted that the rejection is provisional inasmuch as neither application has issued. At this time, Applicants intend to abandon the 08/179,106 application upon the allowance of this application.

Objection to the specification under 35 U.S.C. § 112, first paragraph

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e., failing to provide an enabling disclosure.

The Examiner states that the specification is not enabling for the use of the claimed invention because there is insufficient guidance of how to use the elected mutant herpesvirus as a vaccine. The Examiner cites Roizman as teaching that an effective herpesvirus should meet several criteria, which include a) avirulence, b) stability, c) the mutant should provide immunity to several viral challenges and d) the mutant should have low pathogenicity and should not be capable of transforming host cells. The Examiner states that the specification does not set forth that the herpesvirus having a mutation

in the ICP8 gene meet the criteria as set forth by Roizman.

Applicants respectfully disagree. Applicants are held to the requirements of 112, first paragraph for patentability, not arbitrary criteria set forth in a reference. The Roizman reference is inaccurate for establishing the threshold standard of enablement (i.e., how to make and/or use the claimed invention). Roizman discusses certain optimal characteristics that a vaccine against HSV-1 and HSV-2 should have (col. 2, line 10).

Under 35 U.S.C. § 112 Applicants must provide a written description of the invention, and the manner and process of making it in full, clear, concise and exact terms to enable a person of skill in the art to make and use the invention. Applicants have met the standard under 35 U.S.C. § 112 for providing an enabling disclosure of the claimed invention.

Applicants have described construction and characterization of the claimed mutant herpesvirus having a mutation in genes encoding a protein for viral replication, which renders the herpesvirus replication defective (specification, pp. 16-40). As described on pages 34-35, Applicants demonstrate that herpesviruses having a mutation in the ICP8 gene were unable "to replicate in Vero cells and required complementation by the wild type copy of the ICP8 gene". As such, the specification teaches and exemplifies how to make the mutated herpesviruses employed in the claimed invention. The Examiner does not appear to disagree that the specification is enabling for this aspect of the invention as claimed.

Furthermore, Applicants teach and have demonstrated how to use the replication-defective viruses as claimed. The claimed vaccines are "used" by simply administering the vaccine to an appropriate mammal (such as a human).

Routes of administration are discussed at page 15 of the specification. Applicants have further shown that upon administration to a mammal, the replication-defective herpesviruses effect an antibody subclass shift of IgG2a/IgG (specification, pp. 46-55), induce production of IFN-γ (specification, p. 52) and induce an immunological protective effect (specification, pp. 40-46 and 55-61). With regard to the latter property (the utility questioned by the Examiner), the fact that the mutated herpesvirus of the claims induces an immunological protective effect against infection supports the conclusion and claimed use of the composition as a vaccine.

However, even if Applicants were held to the criteria set forth in Roizman in order to satisfy the requirements of 35 U.S.C. § 112, Applicants have met this burden using experiments similar to those described in the Roizman patent. Specifically, Applicants have shown that the replication defective herpesviruses are a) avirulent (see Roizman, Example 2). As described by Applicants on page 43, lines 10-13.

> Mice which received as much as 10^8 pfu of each mutant appeared healthy and were unaffected by the viruses. Littermates which received 10^7 pfu of wild-type HSV-1 all died.

Applicants also describe b) the stability of the replication defective herpesviruses (i.e., the virus should not revert to the virulent state). As discussed above, Applicants demonstrate that herpesviruses having a mutation in the ICP8 gene were unable "to replicate in Vero cells and required complementation by the wild type of the ICP8 gene". As further stated by Applicants in the specification, since the replication defective herpesviruses "cannot produce progeny viruses, they are substantially safer than conventional attenuated live virus vaccines" (e.g., the Roizman mutant viruses). The replication-defective viruses of the present invention

cannot replicate in cells which do not express a wild type complementing form of the gene, and therefore, cannot spread beyond the site of initial infection. Consistent with this characteristic of the mutant herpesviruses, Applicants show that latent infections were not observed in mice (Specification, p. 46, lines 3-22).

Another Roizman criteria which Applicants have met, is that the replication defective herpesviruses provide c) demonstrated immunity to massive challenges of wild type strains of both HSV-1 and HSV-2. Applicants direct the Examiner's attention to Roizman's criteria that the protection is to "massive" challenges of wild type virus (see Roizman, col. 2, lines 12-13), not "several" challenges of wild type virus, as suggested in the Office Action. As in the Roizman patent (Example 3), Applicants demonstrate reproducibly that mice inoculated with replication defective herpesviruses were protected against challenge with a lethal dose of wild type virus, "in that their survival rate was 100%" (see p. 45, lines 1-28).

Finally, as in the Roizman patent (Example 2), Applicants have demonstrated that the claimed replication-defective viruses have d) low pathogenicity. As described in the specification, mice receiving as much as 10^8 pfu of each mutant herpesvirus were healthy and unaffected by the virus (see p. 43, lines 5-13).

As pointed out by the Examiner, Roizman state that a "desirable property of potential HSV vaccines is that they <u>should</u> not contain transforming domains" (Roizman, col. 5, lines 3-4, emphasis added). Thus, Roizman does not describe this as an essential characteristic of potential HSV vaccines. In fact, Roizman does not demonstrate that his claimed HSV vaccines possess this "desirable" property. Rather, Roizman merely states that all the transforming regions in HSV-2 genome are mapped in the L component of HSV-2 DNA, the corresponding regions of the

HSV-1 genome do not confer transforming properties and the DNA fragment carrying the D and G genes used in the HSV vaccines does not contain sequences which transform cells in culture (Roizman, col. 5, lines 8-15). It is known that transforming domains are present in the HSV-1 genome (see Camacho, A. and P.G. Spear, *Cell, 15*:993-1002, which is being filed as the Exhibit). However, Roizman has not demonstrated the absence of these domains in his claimed HSV vaccines.

Furthermore, Applicants do not believe that the herpesvirus mutations employed herein result in transformation of cells. In fact, since the cells which are infected by the herpesvirus ultimately die, any transformation which may occur is immaterial to the health of the animal.

The Examiner further states that the claimed invention encompasses any mutated herpesvirus having a mutation in the ICP8 gene and it would not be expected that all such mutants of herpesvirus would meet the criteria of Roizman. The Examiner concludes it would be unpredictable and an undue burden for a skilled artisan to determine how to use the mutant herpesvirus as a vaccine.

Applicants disagree that the claims embrace any mutation in the ICP8 gene. The claims include any mutation which results in a defective IPC8 gene, such as a deletion mutation or any other mutation which results in non-functional protein. Many, if not most, mutations embraced within these claims can be immediately envisioned without any screening. That is, removal of the ICP8 gene would be immediately envisioned as rendering the herpesvirus replication defective. Deleting or inserting a nucleotide resulting in an early frame shift in the ICP8 coding region would be immediately envisioned as rendering the herpesvirus replication defective. Any mutations which are questionable can be readily screened for the

presence of ICP8 and/or the ability of the mutant to replicate.

Furthermore, the specification clearly enables the mutation of genes other than ICP8. The specification establishes that mutations in immediate early genes, ICP4 and ICP27 (essential for β and/or γ gene expression) also results in a protective immune response (see page 45).

Even with the above notwithstanding, Applicants respectfully disagree and direct the Examiner's attention to *In re Wands*, wherein the court clearly stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening" (*In re Wands* 8 USPQ2d 1400, 1404 (CAFC 1988)). In *Wands*, the court reversed the PTO's rejection under 35 U.S.C. § 112, first paragraph of appellants' claimed immunoassay method on the grounds that undue experimentation was required to make the high affinity IgM anti-hepatitis B-surface antigen (anti-HBsAG) used in the method. Appellants obtained 143 hybridomas which produced high affinity antibody to HBsAG, nine of which were tested for their ability to produce IgM antibody. Four of the nine hybridomas were found to produce the claimed IgM anti-HBsAg, and the remaining 134 hybridomas were stored.

The PTO stated that there was no proof that the 134 stored hybridomas produced high affinity IgM anti-HBsAg since they were not tested, and thus, were failures. The PTO concluded that only 4 of 143 hybridomas (2.8%) were proven to fall within Appellants' claims and the low success rate demonstrated that a person of skill in the art would have to engage in undue experimentation in order to make the claimed antibodies.

Appellants argued that four out of nine hybridomas which were actually tested were positive, which represents a 44% success rate. Appellants further argued that all the hybridomas were selected for their ability to produce

high binding antibody specific for HBsAg, and it was therefore reasonable to expect, based on known antibody isotype frequency, that some of the hybridomas produce IgM.

The court agreed with appellant. As stated by the court in *Wands*, the test for determining what constitutes undue experimentation

> is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. However, experimentation needed to practice the invention must not be undue experimentation (*Wands* at 1404).

The court noted that appellants' disclosure provided considerable direction and guidance on how to practice the invention and presented working examples. The court also noted that there was a high level of skill in the art at the time the application was filed, and all of the methods needed to practice the invention were well known. Thus, although a person of skill in the art could not reasonably predict which, if any, of the 134 stored hybridomas would produce high affinity IgM anti-HBsAg antibody, the outcome could be determined using routine experimentation. As stated by the court in *Wands*, "Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody" (*In re Wands* at 1406). In addition the court in *Wands* recognized that "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal against a particular antigen" (*In re Wands* at 1407). The court in *Wands* concluded that the "amount of

effort to obtain such antibodies is not excessive" (In re *Wands* at 1407).

Similarly in the present case, Applicants have provided considerable direction, guidance and working examples for preparing replication-defective herpesviruses and screening the mutant herpesviruses in order to find those which are replication defective and can effect an antibody subclass shift of IgG2a/IgG, induce production of IFN-γ and/or induce an immunological protective effect upon administration to a mammal.

The Examiner states that a deposit of herpesvirus d301 is required to enable the invention of Claim 30. Claim 30 has been canceled, without prejudice, as well as other claims reciting the specific herpesvirus mutants described herein.

Thus, Applicants have provided an enabling disclosure for the claimed invention as required for patentability under 35 U.S.C. § 112.

Rejection of Claims 1-26 and 29-32 under 35 U.S.C. § 112, first paragraph

Claims 1-26 and 29-32 are rejected under 35 U.S.C. § 112, first paragraph for the reasons set forth in the objection to the specification.

As discussed above, Applicants have provided an enabling disclosure.

Rejection of Claims 1-26 and 29-32 under 35 U.S.C. § 103

Claims 1-26 and 29-32 are rejected under 35 U.S.C. § 103 as being unpatentable over Roizman and further in view of Gao *et al.* and Weller *et al.* The Examiner states Roizman teaches recombinant herpes simplex virus genomes which contain mutations in portions of the genome responsible for variants and that such viruses may be useful not only as vaccines but as vectors for insertion

of foreign genes. The Examiner states that Roizman does not teach a mutant incapable of replication. The Examiner states that Gao *et al.* describe several mutant herpesviruses of the ICP8 which lack the ability to replicate and bind DNA. The Examiner states that Gao *et al.* describe a mutant d301 from HSV which is replication defective. The Examiner states that the importance of the ICP8 gene product in DNA binding which results in replication and transformation is suggested by Weller *et al.* The Examiner concludes that it would have been obvious to one of ordinary skill in the art to combine the teachings of Roizman on mutant herpesvirus suitable for vaccine and vector purposes with the teaching of Gao *et al.* on mutants of the ICP8 defective in DNA binding and replication and Weller *et al.* on the suggested role of DNA binding protein and transformation in tumorigenicity to develop a vaccine which includes a mutant herpesvirus of the ICP8 or mutant herpesvirus coding for one or more heterologous genes.

Applicants respectfully disagree with the Examiner. As the Court of Appeals for the Federal Circuit has stated

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art... Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. (*In re Dow Chemical*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988)).

In the present case, Applicants describe a replication defective herpesvirus which is mutated in "at least one gene encoding a protein essential for replication of the virus". Applicants' mutant herpesvirus can infect a host but the infection <u>will not produce progeny</u> in the host. However, Applicants' replication-defective herpesviruses

elicit a protective immune response via virally induced or encoded immunogens produced by the infected cells (specification, p.2, line 34 - p. 3, line 1) and an immunomodulatory effect.

In contrast, Roizman describes an attenuated herpesvirus wherein a portion of the HSV-1 genome responsible for neurovirulence "yet nonessential for growth is deleted" (Roizman, abstract). Thus, unlike Applicants' replication-defective viruses, the attenuated herpesvirus taught by Roizman infects the host and multiplies to produce attenuated herpesvirus in the host in order to provide protection against wild type HSV (See Example 1 of Roizman). There is clearly no suggestion in Roizman to use replication-defective herpesviruses as vaccines for HSV-1 or HSV-2. As noted by the Examiner, "Roizman does not teach a mutant incapable of replication" (Office Action, p. 8). In fact, Roizman expressly teaches away from the claimed invention.

The remaining references cited by the Examiner do not make up for the deficiencies of Roizman. Gao *et al.* isolated several mutant herpes simplex viruses mutated in the ICP8 gene to "define the functional domains of ICP8, the major viral DNA-binding protein" (Gao *et al.*, abstract). The results described in the Gao *et al.* reference indicate that DNA binding and nuclear localization functions of ICP8 are genetically independent and that ICP8 specifies nuclear functions in addition to DNA binding. Gao *et al.* state that analysis of ICP8 mutants "will provide a more detailed definition of the ssDNA-binding domain and its role in viral DNA replication and the nature of the other nuclear functions of ICP8" (Gao *et al.*, p. 5265, col 2). There is no mention in Gao *et al.* of using such mutated herpesviruses for any other purpose (e.g., vaccines).

Weller *et al.* describe intra- and intertypic complementation tests with a series of DNA-negative temperature sensitive mutants of HSV-1 and HSV-2. Weller *et al.* state that the data indicate that mutants in particular complementation groups (i.e., 1-1, 2-2) "define the gene for the major herpes simplex virus DNA-binding protein, an early gene product required for viral DNA synthesis" (Weller *et al.*, abstract). Weller *et al.* further state that "Mutants with mutations affecting the expression of the DNA-binding protein should prove useful in elucidating the functions of this protein both in the viral replicative process and in transformation" (Weller *et al.*, p. 264, col. 2). However, there is no mention in Weller *et al.* of using herpesvirus mutants for any other purpose.

There is clearly no suggestion in any of the references cited by the Examiner to generate replication-defective herpesviruses in order to effect an antibody subclass shift of IgG2a/IgG, induce production of IFN-γ and/or induce an immunological protective effect upon administration to a mammal. The court has made it equally clear that

> The mere fact that it is <u>possible</u> to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination (*In re Grabiak*, 226 USPQ 870 at 872 (Fed. Cir., 1985))

Furthermore, even if the combination of Roizman, Gao *et al.* and Weller *et al.* were made, it would not render the claimed invention obvious. At the time of Applicants' invention, replication-defective herpesviruses were not considered suitable vaccine candidates by those of skill

in the art. As indicated in a textbook published as late as 1994,

> The most successful viral vaccines are live avirulent mutants.....The key to their success is the fact that the live virus multiplies in the recipient, eliciting a lasting immune response but causing little or no disease (David O. White and Frank J. Fenner, *Medical Virology*, Academic press 1994, emphasis added, see Chapter 13, p. 219, which is being filed with this Amendment as Exhibit A).

Indeed, this teaching is consistent with the teachings of Roizman. Roizman clearly state that the mutation must be made in a gene "nonessential for growth." Additional evidence that at the time of Applicants' invention, replication-defective herpesviruses were not considered suitable vaccine candidates to a person of skill in the art is provided in Farrell *et al.*, *J. of Virol.*, *68*:927-932 (1994), which is being filed as Exhibit B. Citing the Nguyen *et al.* reference (a paper, co-authored by Dr. David Knipe and Dr. Robert Finberg, which is a publication of some of the work described in the subject application), Farrell *et al.* note that HSV-1 mutants lacking the ICP8 gene were shown capable of protecting mice from subsequent lethal challenge with wild type HSV. However, Farrell *et al.* state that

> Replication-incompetent viruses of this type, however, fail to replicate the viral genome and, in consequence, do not synthesize significant quantities of late proteins, many of which are known to elicit protective immune responses (Farrell *et al.*, p. 927).

Of course, Applicants have shown that the viruses of the claimed invention do indeed, induce a protective immune response. As discussed above, none of the references cited by the Examiner contain the suggestion to one of ordinary skill in the art that replication-defective herpesviruses should be produced to induce an

immunological protective effect, as required under 35 U.S.C. §103. Thus, references do not render Applicants' invention obvious to a person of skill in the art. As discussed above, at the time of Applicants' invention, it was not expected that replication-defective herpesviruses would be suitable for use as vaccines.

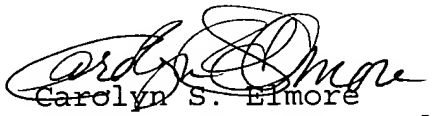
Furthermore, none of the references teach the use of the mutated herpesviruses of the claims, or any other product, to induce IFN-γ or an antibody subclass shift in therapy, particularly in the treatment of herpetic stromal keratitis. As such, Claims 12-22 are separately patentable over the cited references.

SUMMARY

The claims are in condition for allowance in view of the amendments made herein and the comments offered above. Thus, the Examiner is respectfully requested to reconsider the rejections and withdraw them.

If the Examiner believes that a telephone conversation with Applicants' Agent would be helpful in expediting the prosecution of this application, the Examiner is requested to call Applicants' Agent at (617) 861-6240.

Respectfully submitted,



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